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EXAMINER

RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
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1652

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/532,053	Applicant(s) MAKEYEV ET AL.	
	Examiner DELIA M. RAMIREZ	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 July 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 42-81 is/are pending in the application.
- 4a) Of the above claim(s) 42-63,65-67,70-75 and 81 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 64,68,69 and 76-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 April 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/21/05</u> . | 6) <input checked="" type="checkbox"/> Other: <u>alignments</u> . |

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DETAILED ACTION

Status of the Application

Claims 42-81 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

Applicant's election with traverse of Group II, claims 64, 68-69, 76-80, drawn to an isolated polypeptide, a kit comprising said polypeptide and a method to recombinantly produce said polypeptide, as submitted in a communication filed on 7/24/2008 is acknowledged.

Applicant traverses the restriction requirement on the grounds that (1) Chu et al. fail to teach a polymerase that does not require a primer for initiation of RNA synthesis, which is the polymerase of the present invention, (2) the goal in the reference of Chu et al. is replicating a target nucleic acid in a biological sample by using a polymerase which replicates one and the same short segment of a nucleic acid, whereas the polymerase of the instant application is capable of producing template length copies and short complementary RNA copies of a nucleic acid template scattered throughout the entire template length, and (3) the election of a subgroup is unwarranted because the recited nucleic acids share a common feature, namely their encoding of a unique RNA polymerase.

Applicant's arguments have been fully considered. Upon conducting a sequence search, it has been found that the polypeptide of SEQ ID NO: 4 (1026 amino acids) is a fragment of the polypeptide of SEQ ID NO: 2 (1402 amino acids). Similarly, the polynucleotide of SEQ ID NO: 3 (3078 nucleotides) is a fragment of the polynucleotide of SEQ ID NO: 1 (4206 nucleotides). As such, the additional subgroup election requirement to a single sequence is hereby withdrawn. With regard to the teachings of Chu et al., it is noted that (1) there is no requirement in the method of claim 42 for a polymerase which does not require a primer for the initiation of RNA synthesis, and (2) the requirement for producing template-length complementary RNA copies is optional in claim 42. Thus, contrary to applicant's assertion, the

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technical feature of the method of claim 42 was known in the art at the time the invention was made. Furthermore, even if the argument is made that the teachings of Chu et al. do not render the technical feature of the method of claim 1 not novel, the technical feature linking Groups I-V is a polymerase that can produce (1) short complementary RNA copies of a template which are scattered throughout the entire template length, and (2) template length complementary RNA copies of a template. This technical feature is shown by Macino et al. (WO 00/50581, published 8/31/2000; cited in the IDS) to lack novelty or inventive step since Macino et al. teach a polypeptide which is identical to the polypeptide of SEQ ID NO: 2. Since the specification teaches that the polypeptide of SEQ ID NO: 2 is a polymerase that can produce short complementary RNA copies of a template which are scattered throughout the entire template length, and template length complementary RNA copies of a template, the polypeptide of Macino et al. would inherently have that activity. See attached alignment. Thus, the technical feature linking Groups I-V does not make a contribution over the prior art and the claimed inventions do not meet the requirement of unity of invention under PCT Rule 13.2.

The requirement is deemed proper and therefore is made FINAL.

Claims 42-63, 65-67, 70-75, 81 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 64, 68-69, 76-80 are at issue and are being examined herein.

Specification

1. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See, particularly, page 6, last line. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.
2. The specification is objected to for the following reasons. The specification on page 17, third paragraph, and page 18, first paragraph, refers to positions 709-1402 of SEQ ID NO: 4. It is noted

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however that the sequence listing indicates that SEQ ID NO: 4 contains 1026 amino acids. Appropriate correction is required.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/419,562 filed on 10/21/2002.
4. This application is the US national stage of PCT/FI03/00776 filed on 10/17/2003.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 4/21/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

6. The drawings submitted on 4/21/2005 have been reviewed and are accepted by the Examiner for examination purposes.

Claim Objections

7. Claim 64 is objected to due to the recitation of “an isolated polypeptide characterized in that..”. To be consistent with commonly used claim language, it is suggested the term be amended to recite, for example, “an isolated polypeptide wherein...”. Appropriate correction is required.
8. Claims 64 and 80 are objected to due to the recitation of “an amino acid sequence, which shows at least 50% identity to...”. To be consistent with commonly used claim language, it is suggested the

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term be amended to recite "an amino acid sequence, which is at least 50% identical to....". Appropriate correction is required.

9. Claims 68-69 are objected to as being dependent upon a non-elected invention (Group III). For examination purposes, the Examiner will interpret claim 68 as being an independent claim which recites all the limitations of claim 67 which are applicable to the claimed invention.

10. Claim 80 is objected to due to the recitation of "additionally comprising a standard nucleic acid preparation (or preparations) with characterized capacity to serve as template (templates) for RNA synthesis". To be clear and consistent with commonly used claim language, it is suggested the term be amended to recite, for example, "additionally comprising a template for RNA synthesis". Appropriate correction is required.

11. Claim 80 is objected to due to the recitation of "by the polypeptide characterized in that (i).....(f)... SEQ ID NO: 2" because the term is redundant. The kit is required to have the polypeptide of claim 64, which already recites the term "by the polypeptide characterized in that (i).....(f)... SEQ ID NO: 2". Thus, the term is not further limiting the claim and is merely reiterating a limitation already included by virtue of the claim's dependency on claim 64. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 64, 68-69, 76-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claims 64 and 80 (claims 68-69, 76-79 dependent thereon) are indefinite in the recitation of "said polypeptide has sufficient RNA polymerase activity and is capable, when contacted with a nucleic acid

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template ...” for the following reasons. The term “sufficient” is a relative term which is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree. As such, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

15. Claims 64 and 80 (claims 68-69, 76-79 dependent thereon) are indefinite in the recitation of “polypeptide has enhanced solubility resulting in at least 3 times higher yield of the active polymerase” for the following reasons. The term is indefinite in the absence of the conditions which would result in “enhanced” solubility and higher yield. While one could find a protein to be soluble under certain conditions, that same protein may be insoluble under others. In addition, the term “at least 3 times higher yield of the active polymerase” is unclear because the basis for comparison is variable. The yield for the polypeptide of SEQ ID NO: 2 in an active form would vary depending on the conditions under which this polypeptide is made. Therefore, one could have a protein X which meets the limitation of “3 times higher yield” if the comparison is made with the yield for the polypeptide of SEQ ID NO: 2 when made in *E. coli* at growth conditions Y and at the same time not meet the limitation if the comparison is made with the yield for the polypeptide of SEQ ID NO: 2 when made in *E. coli* at growth conditions Z. Also, one could have soluble protein X in *E. coli* grown at conditions Y and not have soluble protein X in *E. coli* grown at conditions Z. For examination purposes, no patentable weight will be given to the entire term recited in (ii). Correction is required.

16. Claims 64 and 80 (claims 68-69, 76-79 dependent thereon) are indefinite in the recitation of “nucleic acid sequence hybridizing to the nucleic acid sequence of....under stringent conditions” for the following reasons. The term “stringent conditions” is indefinite because it is unclear which polynucleotide is recited absent a statement of the experimental conditions under which the hybridization reaction is performed. Nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions. The art does not recognize a single set of experimental conditions as “stringent” and even the specification indicates that there are different degrees of stringency

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(high stringency, page 19, last two lines, page 20, lines 1-5). The specification does not define the conditions which are considered stringent. It should also be noted that since nucleic acid sequences are graphical representations of the order in which nucleotides are arranged in a nucleic acid molecule, and hybridization is a process that occurs between nucleic acid molecules, hybridization cannot occur between sequences. For examination purposes, it will be assumed that the term “stringent conditions” reads “any hybridization conditions”. Correction is required.

17. Claims 64 and 80 (claims 68-69, 76-79 dependent thereon) are indefinite in the recitation of “(e) a nucleic acid sequence encoding a polypeptide comprising the amino acids 709 to 1402 of SEQ ID NO: 4 or any sequence longer than that up to the sequence comprising....” for the following reasons. First, SEQ ID NO: 4 has only 1026 amino acids according to the sequence listing. As such, it is unclear which fragment of SEQ ID NO: 4 is being referred to. In addition, even if it is assumed that SEQ ID NO: 4 has at least 1402 amino acids, the term “amino acids 709 to 1402 of SEQ ID NO: 4 or any sequence longer than that up to the sequence comprising the amino acids 2 to 1402 of SEQ ID NO: 2” is indefinite because it is unclear if the “sequence longer than that up to...” being referred to is (1) any sequence completely unrelated to SEQ ID NO: 4 or 2 which is longer than 694 amino acids (694 = length of fragment 709-1402 of SEQ ID NO: 4), or (2) any sequence within SEQ ID NO: 4 which comprises amino acids 709 to 1402 of SEQ ID NO: 4 wherein said sequence is longer than 694 amino acids. It is also noted that by setting the length limit to “the sequence comprising the amino acids 2 to 1402 of SEQ ID NO: 2”, the claim is not setting the upper length limit to 1401 amino acids (1401 = length of fragment 2-1402 of SEQ ID NO: 2) since the term “comprising” is open language. As such, a sequence comprising amino acids 2 to 1402 of SEQ ID NO: 2 can have any length beyond 1401 amino acids. For examination purposes, it will be assumed that the term reads “(e) a nucleic acid sequence encoding a polypeptide comprising amino acids 709 to 1402 of SEQ ID NO: 2, or amino acids 2 to 1402 of SEQ ID NO: 2”. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 64, 68-69, 76-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 64, 68-69, 76-80 encompass a genus of proteins having RNA polymerase activity wherein said proteins produce short complementary RNA copies of a template scattered throughout the template, or template-length complementary RNA copies of a template, wherein said proteins are encoded by nucleic acids which hybridize to a polynucleotide encoding the polypeptide of SEQ ID NO: 4 under any hybridization conditions, or wherein said proteins are encoded by polynucleotides encoding polypeptides having at least 50% sequence identity to the polypeptide of SEQ ID NO: 2. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials”. As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed

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correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

While the specification in the instant application discloses the structure of a single species of the recited genus of proteins having RNA polymerase activity and able to produce (i) short complementary RNA copies of a template scattered throughout the template, and (ii) template-length complementary RNA copies of a template, i.e. the polypeptide of SEQ ID NO: 2, as well as a fragment of said polypeptide which retains the recited activity, i.e., the polypeptide of SEQ ID NO: 4, it provides no clue as to the structural elements required in any protein having the recited RNA polymerase activity, nor does it teach which structural elements within the polypeptide of SEQ ID NO: 2 are required in any protein having the recited RNA polymerase activity. Furthermore, there is no teaching in the specification or the art as to a correlation between structure and the desired RNA polymerase activity.

The claim encompasses a large genus of proteins sharing a limited amount of structural features. A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, the recited structural feature, i.e., "50% sequence identity to SEQ ID NO: 2", "hybridization under any conditions", is not representative of all the members of the genus of proteins recited since there is no information as to which are the structural elements within the polypeptide of SEQ ID NO: 2 that are essential for the recited activity, which are the remaining structural elements required in the recited polypeptides in addition to those recited in the claims such that the desired RNA polymerase activity is displayed, or a correlation between structure and function which would provide

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those unknown structural features. In addition, while one could argue that SEQ ID NO: 2 is representative of the structure of all the members of the genus, such that the recited genus of polypeptides is adequately described by the disclosure of the structure of the polypeptide of SEQ ID NO: 2, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in activity. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teach that one conservative amino acid substitution transforms a β -ketoacyl synthase into a malonyl decarboxylase and completely eliminates β -ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teach that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes to a polypeptide may result in changes affecting function, and no additional information correlating structure with the desired RNA polymerase activity has been provided, one cannot reasonably conclude that SEQ ID NO: 2 is representative of the structure of all proteins having the recited RNA polymerase activity which are required by the claims.

Due to the fact that the specification only discloses a single species of the genus, i.e. the polypeptide of SEQ ID NO: 2, and the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

20. Claims 64, 68-69, 76-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 2 and the polypeptide of SEQ ID NO: 4, as well as kits comprising the polypeptides of SEQ ID NO: 2 or 4, does not reasonably provide enablement for (1) a polypeptide having RNA polymerase activity, wherein said polypeptide produces short complementary RNA copies of a template scattered throughout the template or template-length complementary RNA copies of a template, wherein said polypeptide is encoded by nucleic acids which

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hybridize to a polynucleotide encoding the polypeptide of SEQ ID NO: 4 under any hybridization conditions, or wherein said polypeptide is encoded by polynucleotides encoding polypeptides having at least 50% sequence identity to the polypeptide of SEQ ID NO: 2, or (2) kits comprising the polypeptide of (1). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 64, 68-69, 76-80 are so broad as to encompass (1) any polypeptide having RNA polymerase activity, wherein said polypeptide produces (i) short complementary RNA copies of a template scattered throughout the template, or (ii) template-length complementary RNA copies of a template, wherein said polypeptide is encoded by nucleic acids which hybridize to a polynucleotide encoding the polypeptide of SEQ ID NO: 4 under any hybridization conditions, or wherein said polypeptide is encoded by polynucleotides encoding polypeptides having at least 50% sequence identity to the polypeptide of SEQ ID NO: 2, and (2) kits comprising the polypeptide of (1). The enablement provided is not commensurate in scope with the claim due to the extremely large number of proteins of unknown structure encompassed by the claims. In the instant case, the specification enables a single species, i.e., the polypeptide of SEQ ID NO: 2, and its functional fragment, the polypeptide of SEQ ID NO: 4.

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The amount of direction or guidance presented and the existence of working examples. The specification discloses the amino acid sequence of a single protein as a working example (SEQ ID NO: 2) and provides a single fragment which was shown to display the same enzymatic activity, i.e., the polypeptide of SEQ ID NO: 4. However, the specification fails to provide any clue as to the structural elements required in any protein having the recited RNA polymerase activity, or which are the structural elements in the polypeptide of SEQ ID NO: 2 which are essential for any protein to display the recited RNA polymerase activity. No correlation between structure and function has been presented. There is no information or guidance as to which amino acid residues in the polypeptide of SEQ ID NO: 2 can be modified and which ones are to be conserved to create a variant displaying the same activity as that of the polypeptide of SEQ ID NO: 2.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The amino acid sequence of a polypeptide determines its structural and functional properties. While the art discloses several proteins having RNA polymerase activity, neither the specification nor the art provide a correlation between structure and RNA polymerase activity such that one of skill in the art can envision the structure of any RNA polymerase protein that produces (i) short complementary RNA copies of a template scattered throughout the template, and/or (ii) template-length complementary RNA copies of a template. In addition, the art does not provide any teaching or guidance as to (1) which changes can be made to the protein of SEQ ID NO: 2 such that the resulting variant would display the same RNA polymerase activity found in the polypeptide of SEQ ID NO: 2, or (2) the general tolerance of RNA polymerases to structural modifications and the extent of such tolerance. The art clearly teaches that modification of a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are tolerant of modification and which ones are conserved is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide

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will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for any number of polypeptides and determine which ones have the desired activity. The total number of variants of a polypeptide having a specific sequence identity can be calculated from the formula $N! \times 19^A / (N-A)! / A!$, where N is the length in amino acids of the reference polypeptide and A is the number of allowed substitutions for a specific % identity. Thus, for a variant of the polypeptide of SEQ ID NO: 2 having 50% sequence identity to SEQ ID NO: 2, the total number of variants to be tested is $1402! \times 19^{701} / (1402-701)! / 701!$ (SEQ ID NO: 2 has 1402 amino acids; 701 amino acids = 0.5x1402) or 6.03×10^{1316} variants. This number would be even greater for a polypeptide which is encoded by a nucleic acid which hybridizes under any conditions to a polynucleotide encoding the polypeptide of SEQ ID NO: 2 in view of the fact that the % identity in that case is potentially lower. In the absence of (1) a rational and predictable scheme for modifying any residue in the polypeptide of SEQ ID NO: 2 such that the resulting variant would maintain the same RNA polymerase activity, and/or (2) a correlation between structure and the ability to produce (i) short complementary RNA copies of a template scattered

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throughout the template, and/or (ii) template-length complementary RNA copies of a template, one of skill in the art would have to test an essentially infinite number of proteins to determine which ones have the desired activity. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Therefore, taking into consideration the extremely broad scope of the claim, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and the desired function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 64, 68-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Macino et al. (WO 00/50581 published 8/31/2000; cited in the IDS).

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Claim 64 is directed in part to a polypeptide encoded by (1) a nucleic acid comprising SEQ ID NO: 3, (2) a nucleic acid encoding amino acids 2-1402 of SEQ ID NO: 2, or (3) a nucleic acid which encodes a polypeptide having at least 50% sequence identity to SEQ ID NO: 2, wherein said polypeptide has RNA polymerase activity and is able to produce (i) short complementary RNA copies of a template scattered throughout the template, and/or (ii) template-length complementary RNA copies of a template. Claims 68-69 are directed in part to a method to recombinantly produce the protein of claim 64 by culturing a host cell transformed with a vector comprising a nucleic acid encoding the protein of claim 64, and recovering said protein from the cell or culture medium. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

Macino et al. teach an RNA polymerase polypeptide (SEQ ID NO: 2 in that reference) which is soluble (page 18, line 4) and identical in size and sequence to the polypeptide of SEQ ID NO: 2 of the instant application. Macino et al. also teach a polynucleotide encoding said polypeptide (SEQ ID NO: 1 in that reference), host cells and vectors comprising said polynucleotide as well as a recombinant method to produce said polypeptide (page 8, line 23-page 9, line 28). See attached alignment. Since the specification of the instant application discloses that the polypeptide of SEQ ID NO: 2 is able to produce (i) short complementary RNA copies of a template scattered throughout the template, and/or (ii) template-length complementary RNA copies of a template, the polypeptide of Macino et al. would have the same functional properties in view of the fact that its amino acid sequence is identical to that of the polypeptide of SEQ ID NO: 2. Therefore, the teachings of Macino et al. anticipate the instant claims as written.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill

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in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 76-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Macino et al. (WO 00/50581 published 8/31/2000; cited in the IDS). The teachings of Macino et al. have been discussed above. Macino et al. do not teach a kit comprising the RNA polymerase.

Claims 76-80 are directed in part to a kit comprising the polypeptide of claim 64 as described above, as well as labeled nucleoside triphosphates for RNA synthesis and nucleic acids which can serve as templates for RNA synthesis.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to assemble a kit comprising the polypeptide of Macino et al., a nucleic acid template, and labeled nucleoside triphosphates for RNA synthesis. A person of ordinary skill in the art is motivated to make such kit for the benefit of having the main components required to test the enzymatic activity of the protein of Macino et al. readily available such that further functional characterization of the protein of Macino et al. can be carried out. One of skill in the art is motivated to use labeled nucleoside triphosphates because labeled nucleoside triphosphates would allow for easy detection of the reaction products. One of ordinary skill in the art has a reasonable expectation of success at assembling the kit in view of the fact that (1) Macino et al. teach that their protein is an RNA-dependent RNA polymerase, thus, one of skill in the art would have known that a template and labeled nucleoside triphosphates for

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RNA synthesis are among the reagents that would be needed in a kit to characterize the enzymatic activity, and (2) all the materials recited in the kit are available. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

26. No claim is in condition for allowance.

27. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez
Primary Patent Examiner
Art Unit 1652

DR
November 12, 2008